

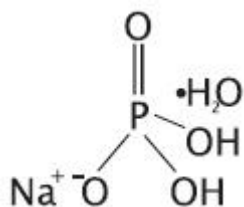
VISICOL - sodium phosphate, monobasic, monohydrate and sodium phosphate, dibasic anhydrous tablet
Salix Pharmaceuticals, Inc.

DESCRIPTION

Visicol[®] (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP) is a purgative used to clean the colon prior to colonoscopy. Visicol[®] Tablets are white to off-white compressed tablets, with a monogram "I" on each side of the upper surface and a plain lower surface. Each tablet contains 1.102 grams of sodium phosphate monobasic monohydrate, USP and 0.398 grams of sodium phosphate dibasic anhydrous, USP for a total of 1.5 grams of sodium phosphate per tablet. Inert ingredients include microcrystalline cellulose (MCC), NF; magnesium stearate, NF; and colloidal silicon dioxide, NF. Visicol[®] is gluten-free.

The structural and molecular formulae and molecular weights of the active ingredients are shown below:

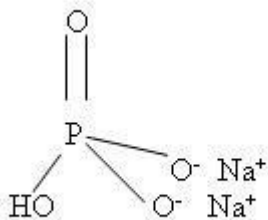
- Sodium phosphate monobasic monohydrate, USP



Molecular Formula: $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$

Molecular Weight: 137.99

- Sodium phosphate dibasic anhydrous, USP



Molecular Formula: Na_2HPO_4

Molecular Weight: 141.96

Visicol[®] Tablets are for oral administration only.

CLINICAL PHARMACOLOGY

Visicol[®] Tablets, taken in two doses of 30 grams (the complete regimen contains a total of 60 grams of sodium phosphate) approximately twelve hours apart, induces diarrhea, which effectively cleanses the entire colon. Each administration has a purgative effect for approximately 1 to 3 hours. The primary mode of action is thought to be through osmotic action of sodium, causing large amounts of water to be drawn into the colon, promoting colon evacuation.

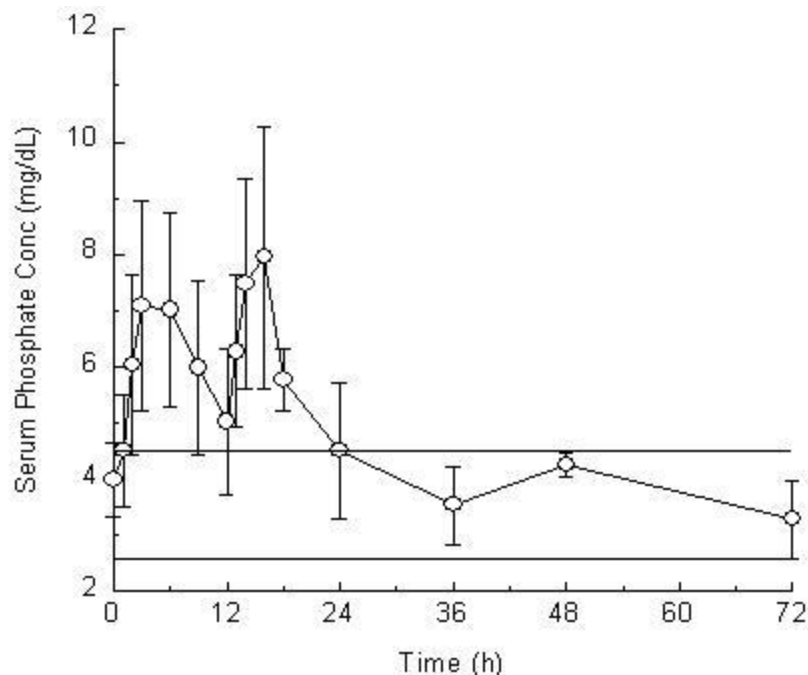
Pharmacokinetics

An open-label pharmacokinetic study of Visicol[®] in healthy volunteers was performed to determine the concentration-time profile of serum inorganic phosphorus levels after Visicol[®] administration. All subjects received a total of 60 grams of sodium phosphate with a total liquid volume of 3.6 quarts. Subjects received a 30 gram dose (20 tablets given as 3 tablets every 15 minutes with 8 ounces of clear liquids) beginning at 6 PM and then received a second 30 gram dose (20 tablets given as 3 tablets every 15 minutes with 8 ounces of clear liquids) the following morning beginning at 6 AM.

Twenty-three healthy subjects (mean age 57 years old; 57% male and 43% female; and 65% Hispanic, 30% Caucasian, and 4% African-American) participated in this pharmacokinetic study. The serum phosphorus level rose from a mean (\pm standard deviation) baseline of 4.0 (\pm 0.7) mg/dL to 7.7 (\pm 1.6 mg/dL), at a median of 3 hours after the administration of the first 30 gram dose of

Visicol[®] Tablets (see Figure 1).

Figure 1. Mean (\pm standard deviation) serum phosphorus concentrations



The serum phosphorus level rose to a mean of $8.4 (\pm 1.9)$ mg/dL, at a median of 4 hours after the administration of the second 30 gram dose of Visicol® Tablets. The serum phosphorus level remained above baseline for a median of 24 hours after the administration of the initial dose of Visicol® Tablets (range 16 to 48 hours).

The upper (4.5 mg/dL) and lower (2.6 mg/dL) reference limits for serum phosphate are represented by solid bars.

Special Populations

Renal insufficiency: The effect of renal dysfunction on Visicol® Tablets pharmacokinetics has not been studied. Since the inorganic form of phosphate in the circulating plasma is excreted almost entirely by the kidneys, patients with renal disease may have difficulty excreting a large phosphate load. Thus, Visicol® Tablets should be used with caution in patients with impaired renal function (see **WARNINGS**).

Hepatic insufficiency: Visicol® Tablets have not been investigated in patients with hepatic failure. Visicol® is not expected to be metabolized in the liver.

Geriatric: In a single pharmacokinetic study of sodium phosphate tablets, which included 6 elderly volunteers, plasma half-life increased two-fold in subjects > 70 years of age compared to subjects < 50 years of age (3 subjects and 5 subjects, respectively).

Gender: No difference in serum phosphate AUC values were observed in the single pharmacokinetic study conducted with Visicol® in 13 male and 10 female healthy volunteers.

CLINICAL STUDIES

A total of 957 adult patients were enrolled and treated in the controlled clinical trials of Visicol® Tablets. Males and females were about equally represented. Approximately 87% of the study population was Caucasian. Visicol® Tablets were found to be comparable in cleansing efficacy to the comparison drug, a commercially available polyethylene glycol-salt (PEG-salt solution) solution (Cherry Flavor NuLYTELY®). Two identical, single (investigator) blind, randomized, multicenter trials were conducted comparing the efficacy and safety of Visicol® Tablets and the PEG-salt solution comparator as a colon cleansing agent in patients undergoing routine diagnostic colonoscopy. In each study, over 200 patients were randomized to self-administer the Visicol® Tablets and over 200 were randomized to self-administer the PEG-salt solution comparator. Colonoscopy was generally performed within 5 hours of the second dose. Physicians used a four-point, validated Physician Questionnaire to assess efficacy. The distribution of "excellent", "good", "fair" and "inadequate", as evaluated by the physician performing the colonoscopy, was comparable in both groups. Cleansing efficacy observed in these studies is described in Table 1.

Table 1: Observed overall colon cleansing efficacy of Visicol[®] Tablets versus PEG-salt solution comparator in the all assessed patient population

Efficacy Rating	Study A		Study B	
	Visicol Tablets n (%)	PEG-salt solution Comparator n (%)	Visicol Tablets n (%)	PEG-salt solution Comparator n (%)
Excellent or good	171 (82.2)	156 (75.4)	183 (86.3)	170 (78.0)
Fair	34 (16.3)	49 (23.7)	26 (12.3)	45 (20.6)
Inadequate	3 (1.4)	2 (1.0)	3 (1.4)	3 (1.4)
Total patients	208	207	212	218
p value [†]	n.s.		n.s.	

[†] p values (Cochran-Mantel-Haenszel Test) were calculated for comparisons between Excellent and Good versus Fair versus Inadequate; Visicol[®] Tablets versus PEG-salt solution comparator.

The efficacy of overall colonic cleansing with the Visicol[®] Tablets was comparable to the PEG-salt solution. In addition, the incidence of “Inadequate” colon cleansing ratings due to poor purgative preparation was similar between Visicol[®] Tablets and the PEG-salt solution comparator. Also, cleansing efficacy in the ascending colon with Visicol[®] Tablets was comparable to the PEG-salt solution.

INDICATIONS AND USAGE

Visicol[®] Tablets are indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older.

CONTRAINDICATIONS

Visicol[®] Tablets are contraindicated in patients with biopsy-proven acute phosphate nephropathy.

Visicol[®] Tablets are contraindicated in patients with a known allergy or hypersensitivity to sodium phosphate salts or any of its ingredients.

WARNINGS

Administration of sodium phosphate products prior to colonoscopy has resulted in fatalities due to significant fluid shifts, severe electrolyte abnormalities, and cardiac arrhythmias. These fatalities have been observed in patients with renal insufficiency, in patients with bowel perforation, and in patients who misused or overdosed sodium phosphate products.

Considerable caution should be advised before Visicol[®] Tablets are used in patients with the following illnesses: severe renal insufficiency (creatinine clearance less than 30 mL/minute), congestive heart failure, ascites, unstable angina, acute bowel obstruction, bowel perforation, toxic megacolon, gastric retention, ileus, pseudo-obstruction of the bowel, severe chronic constipation, acute colitis, gastric bypass or stapling surgery or hypomotility syndrome.

Consider performing baseline and post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN) in patients who may be at increased risk for serious adverse events, including those with history of renal insufficiency, history of # or at greater risk of # acute phosphate nephropathy, known or suspected electrolyte disorders, seizures, arrhythmias, cardiomyopathy, prolonged QT, recent history of a MI and those with known or suspected hyperphosphatemia, hypocalcemia, hypokalemia, and hypernatremia. Also if patients develop vomiting and/or signs of dehydration then measure post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN).

Renal Disease, Acute Phosphate Nephropathy, and Electrolyte Disorders

There have been rare, but serious reports of renal failure and acute phosphate nephropathy (also known as nephrocalcinosis) in patients who received oral sodium phosphate products (including oral sodium phosphate solutions and tablets) for colon cleansing prior to colonoscopy. These cases often resulted in permanent impairment of renal function and several patients required long-term dialysis. Patients at increased risk of acute phosphate nephropathy may include patients with the following: hypovolemia, baseline kidney disease, increased age, and patients using medicines that affect renal perfusion or function [such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and possibly nonsteroidal anti-inflammatory drugs (NSAIDs)].

Use Visicol[®] with caution in patients with impaired renal function, known or suspected electrolyte disturbances, or people taking concomitant medications that may affect electrolyte levels (such as diuretics). Patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have them corrected before treatment with Visicol[®] Tablets.

Seizures

There have been rare reports of generalized tonic-clonic seizures and/or loss of consciousness associated with use of sodium phosphate products in patients with no prior history of seizures. The seizure cases were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia) and low serum osmolality. The neurologic abnormalities resolved with correction of fluid and electrolyte abnormalities. Visicol[®] should be used with caution in patients with a history of seizures and in patients at higher risk of seizure [patients using concomitant medications that lower the seizure threshold (such as tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, or patients with known or suspected hyponatremia].

Cardiac Arrhythmias

There have been rare, but serious reports of arrhythmias associated with the use of sodium phosphate products. Visicol[®] should be used with caution in patients with higher risk of arrhythmias (patients with a history of cardiomyopathy, patients with prolonged QT, patients with a history of uncontrolled arrhythmias, and patients with a recent history of a myocardial infarction). Pre-dose and post-colonoscopy ECGs should be considered in patients with high risk of serious, cardiac arrhythmias.

PRECAUTIONS

General

Patients should be instructed to drink 8 ounces of clear liquids with each 3-tablet (or each 2-tablet) dose of Visicol[®]. Patients should take a total of 3.6 quarts of clear liquids with Visicol[®]. Inadequate fluid intake, as with any effective purgative, may lead to excessive fluid loss and hypovolemia. Dehydration from purgation may be exacerbated by inadequate oral fluid intake, vomiting, and/or the use of diuretics. Patients should not take additional laxatives or purgatives, particularly additional sodium phosphate-based products.

Prolongation of the QT interval has been observed in some patients who were dosed with Visicol[®] Tablets. QT prolongation with Visicol[®] Tablets has been associated with electrolyte imbalances, such as hypokalemia and hypocalcemia. Visicol[®] Tablets should be used with caution in patients who are taking medications known to prolong the QT interval, since serious complications may occur. Pre-dose and post-colonoscopy ECGs should be considered in patients with known prolonged QT. In these studies, prolongation of the QT interval was also observed in some patients treated with PEG-salt solution.

Patients with a history of swallowing difficulties or anatomic narrowing of the esophagus, such as a stricture, may have difficulty swallowing Visicol[®] Tablets. Undigested or partially digested Visicol[®] Tablets may be seen in the stool or during colonoscopy. In addition, undigested tablets from other medications may be seen in the stool or during colonoscopy.

Administration of Visicol[®] Tablets may induce colonic mucosal aphthous ulcerations, since this endoscopic finding observed with other sodium phosphate cathartic preparations. This colonoscopic finding should be considered in patients with known or suspect inflammatory bowel disease (IBD).

Because published data suggest that sodium phosphate absorption may be enhanced in patients experiencing an acute exacerbation of IBD, Visicol[®] Tablets should be used with caution in IBD patients.

Since Visicol[®] Tablets were not studied in patients who recently had cardiac surgery (including coronary artery bypass graft surgery) Visicol[®] should be used with caution in these patients.

Drug Interactions

Medications administered in close proximity to Visicol[®] Tablets may not be absorbed from the gastrointestinal tract due to the rapid intestinal peristalsis and watery diarrhea induced by the purgative agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Visicol[®]. Studies to evaluate the effect of Visicol[®] on fertility or its mutagenic potential have not been performed.

Pregnancy

Category C. Reproduction studies have not been conducted with Visicol[®]. It is also not known whether Visicol[®] can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Visicol[®] Tablets should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and efficacy of Visicol[®] Tablets have not been demonstrated for patients less than 18 years of age.

Geriatric Use

Of the 980 subjects/patients in the Visicol[®] studies, 284 (29%) subjects/patients were 65 years of age or older. Of the 548 subjects/patients who received Visicol[®] in these studies, 146 (27%) were 65 years of age or older and 42 (8%) subjects/patients were 75 years of age or older.

In two phase 3 Visicol[®] trials (Study A and Study B), no overall differences in safety or effectiveness were observed between geriatric patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out; therefore, Visicol[®] Tablets should be used with caution in geriatric patients.

Sodium phosphate is known to be substantially excreted by the kidney, and the risk of adverse reactions with sodium phosphate may be greater in patients with impaired renal function. Since geriatric patients are more likely to have impaired renal function, consider performing baseline and post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN) in these patients (see WARNINGS).

ADVERSE REACTIONS

In the phase 3 Visicol[®] trials, bloating, nausea, abdominal pain, and vomiting were the most common drug-related adverse events reported with the use of Visicol[®] (see Table 2). Since diarrhea was considered as a part of the efficacy of Visicol[®] diarrhea was not defined as an adverse event in the clinical trials. Small superficial mucosal ulcerations, typical of those previously reported from the use of liquid preparations of sodium phosphate, and instances of mucosal bleeding have been observed on colonoscopy. No patient in the clinical studies developed predefined postural changes in vital signs with concomitant symptoms of lightheadedness or syncope.

Table 2: Frequency of Drug-related* Adverse Events (≥ 2%) of Patients in the Phase 3 Visicol Trials (Studies A and B)

	Visicol[®] %=n/N	NuLYTELY[®] %=n/N
	N=427	N=432
Bloating	47%	61%
Nausea	35%	54%
Abdominal Pain	30%	36%
Vomiting	7%	18%

* Drug-related were adverse events possibly or probably drug-related

Electrolyte Changes

In Visicol[®] trials, changes in serum electrolytes (including phosphate, calcium, potassium, and sodium) have been observed in patients taking Visicol[®] Tablets.

In the Visicol[®] phase 3 trials, 96% and <1% of patients who took Visicol[®] (60 grams) and NuLYTELY[®] (up to 4 liters), respectively, developed hyperphosphatemia (defined as phosphate level > 4.7 mg/dL) on the day of the colonoscopy. In these trials, patients who took Visicol[®] and NuLYTELY[®] had baseline mean phosphate levels of 3.3 and 3.4 mg/dL and subsequently developed on the day of the colonoscopy mean phosphate levels of 7.1 and 3.3 mg/dL, respectively.

Two to three days after colonoscopy, 34%, 66%, and 0% of patients who received Visicol[®] had (reactive) hypophosphatemia (defined as phosphate level > 2.4 mg/dL), normal phosphate levels, and hyperphosphatemia, respectively. Two to three days after colonoscopy, 3%, 96%, and 1% of patients who received NuLYTELY[®] had (reactive) hypophosphatemia normal phosphate levels, and hyperphosphatemia, respectively. Two to three days after colonoscopy, patients who took Visicol[®] and NuLYTELY[®] had mean phosphate levels of 2.6 and 3.3 mg/dL, respectively.

In the Visicol[®] phase 3 trials, 47% and 9% of patients who took Visicol[®] and NuLYTELY[®], respectively, developed hypocalcemia (defined as calcium level < 8.6 mg/dL) on the day of the colonoscopy. The mean changes in calcium levels (from baseline) for the Visicol[®] and NuLYTELY[®] patients were -0.6 and -0.1 mg/dL, respectively. Furthermore, in these trials, 28% and 3% of patients who took Visicol[®] and NuLYTELY[®], respectively, developed hypokalemia (defined as potassium level < 3.5 mEq/L) on the day of the colonoscopy. The mean changes in potassium levels (from baseline) for the Visicol[®] and NuLYTELY[®] patients were -0.5 and -0.1 mEq/L, respectively. None of the patients who developed hypocalcemia or hypokalemia in the trials required treatment.

Post Marketing Reports

There have been spontaneous reports of adverse events with post-marketing use of Visicol[®] Tablets. These include rare reports of hypersensitivity reactions (eg, rash, urticaria, pruritus, tongue edema, throat tightness, and paresthesia of the lips).

There have been reports of acute phosphate nephropathy, acute renal failure, seizures, and cardiac arrhythmias with post-marketing use of Visicol[®] Tablets (see WARNINGS).

OVERDOSAGE

There have been no reported cases of overdose with Visicol[®] Tablets. Purposeful or accidental ingestion of more than the recommended dosage of Visicol[®] Tablets might be expected to lead to severe electrolyte disturbances, including hyperphosphatemia,

hypocalcemia, hypernatremia, or hypokalemia, as well as dehydration and hypovolemia, with attendant signs and symptoms of these disturbances. Certain severe electrolyte disturbances may lead to cardiac arrhythmias, seizure, renal failure, and death. The patient who has taken an overdosage should be monitored carefully, and treated symptomatically for complications until stable.

DOSAGE AND ADMINISTRATION

The recommended dose of Visicol[®] Tablets for colon cleansing for adult patients is 40 tablets (60 grams of sodium phosphate) taken orally with a total of 3.6 quarts of clear liquids in the following manner:

The evening before the colonoscopy procedure: Take 3 Visicol[®] Tablets (the last dose will be 2 Visicol[®] Tablets) with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets.

On the day of the colonoscopy procedure: Starting 3-5 hours before the procedure, take 3 Visicol[®] Tablets (the last dose will be 2 Visicol[®] Tablets) with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets.

It is recommended that patients receiving Visicol[®] be advised to adequately hydrate before, during, and after the use of Visicol[®].

Patients should not use Visicol[®] within seven days of previous administration. No additional enema or laxative is required, and patients should be advised NOT to take additional agents, particularly those containing sodium phosphate.

HOW SUPPLIED

Visicol[®] Tablets are supplied in child-resistant bottles containing 40 tablets and 100 tablets. Each tablet contains 1.102 g sodium phosphate monobasic monohydrate, USP and 0.398 g sodium phosphate dibasic anhydrous, USP for a total of 1.5 g of sodium phosphate per tablet. Each bottle contains two silica desiccant packets, which are not to be ingested.

NDC 65649-601-04 (40 tablets)

NDC 65649-601-41 (100 tablets)

Rx only

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Discard any unused portion.

Manufactured by:

Pharmaceutical Manufacturing Research Services Inc.

Horsham, PA 19044

For:

Salix Pharmaceuticals, Inc.

Morrisville, NC 27560

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Product protected by U.S. Patent No. 5,616,346 and other pending applications.